Epidemiology and Management of Infections after Lung Transplantation

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Abstract: Lung transplantation has become an accepted treatment for end-stage pulmonary parenchymal and vascular diseases. Infections still are the most common cause of early and late morbidity and mortality in lung transplant recipients. Bacterial infections comprise approximately half of all infectious complications. Cytomegalovirus (CMV) infections and disease have become less frequent, because of prophylaxis with ganciclovir. Because CMV is also involved in the pathogenesis of obliterative bronchiolitis, the frequency of this infection may also reduce the occurrence of this main obstacle to successful lung transplantation. Invasive fungal infections remain a problem, but they have also decreased in frequency because of better control of risk factors such as CMV disease and preemptive antifungal therapy. Nonherpes respiratory viral infections have emerged as a serious problem. Their severity may be reduced by treatment with ribavirin. Meticulous postoperative surveillance, however, is still crucial for the management of lung transplant patients with respect to early detection and treatment of rejection and infection

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SUPPLEMENT ARTICLE

Epidemiology and Management of Infections after Lung Transplantation

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Lung transplantation has become an accepted treatment for end-stage pulmonary parenchymal and vascular diseases. Infections still are the most common cause of early and late morbidity and mortality in lung transplant recipients. Bacterial infections comprise approximately half of all infectious complications. Cytomegalovirus (CMV) infections and disease have become less frequent, because of prophylaxis with ganciclovir. Because CMV is also involved in the pathogenesis of obliterative bronchiolitis, the frequency of this infection may also reduce the occurrence of this main obstacle to successful lung transplantation. Invasive fungal infections remain a problem, but they have also decreased in frequency because of better control of risk factors such as CMV disease and preemptive antifungal therapy. Nonherpes respiratory viral infections have emerged as a serious problem. Their severity may be reduced by treatment with ribavirin. Meticulous postoperative surveillance, however, is still crucial for the management of lung transplant patients with respect to early detection and treatment of rejection and infection.

Lung transplantation has become a successful treatment option for end-stage diseases of the lungs and the pulmonary circulation [1, 2]. According to the registry of the International Society for Heart and Lung Transplantation, 1-, 2-, and 5-year survival rates of 74%, 65%, and 47%, respectively, can be achieved [3]. This success is mainly due to careful selection of patients, improved surgical techniques, and organ preservation, as well as sophisticated postoperative management. The most important complications in survivors of the perioperative period of lung transplantation are infections and episodes of acute rejection. The main obstacle to long-term success of lung transplantation, however, remains chronic rejection, which occurs in up to two-thirds of patients [4]. It is characterized histologically by obliterative bronchiolitis and a variable degree of pulmonary vascular involvement. In addition to the number of previous acute rejection episodes and the incidence of persistent rejection after treatment of acute rejection episodes [4], cytomegalovirus (CMV) infection and disease [5] are the most relevant risk factors for the development of obliterative bronchiolitis. Thus, strategies for prophylaxis, as well as early diagnosis and treatment of CMV disease, may be crucial for further improvement of the results of lung transplantation.

Infectious complications are the most common cause of morbidity and mortality at all time points after lung transplantation [6–11] and occur twice as frequently as in heart transplant recipients [7, 9]. At least two-thirds of the infections involve the respiratory tract [8–10]. Infectious complications cause at least half of the deaths after lung transplantation, and more than one-third of these fatal outcomes occur in patients with underlying obliterative bronchiolitis [12]. Possible reasons for this very high incidence of infectious complications are listed in table 1 and include an allograft exposed continuously to the environment, impaired mucociliary clearance, bronchial anastomotic problems, and remaining native lung complications after single-lung transplantation. The most important predisposing con-

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Table 1. Conditions predisposing for infections after lung transplantation.

Lung allograft is continuously exposed to the external environment
Denervation of allograft:
Diminished cough reflex
Abnormal mucociliary clearance
Reactive hyperresponsiveness
Interrupted lymphatic drainage (especially during first weeks)
Anastomosis site:
May enhance colonization
Airway dehiscence and mediastinitis
Bronchial stenosis and postobstructive infection
Acute rejection episodes:
Require enhanced immunosuppression
Inflammatory response at port of entry of infections
Donor lung may transmit infections:
From prolonged mechanical ventilation
From previous inactive infections (tuberculosis, *Candida* and *Aspergillus* species, *Histoplasmosis, Coccimycosis*)
Native lung after single-lung transplantation:
Occult pretransplant infection (tuberculosis, *Aspergillus* species, *Pneumocystis carinii,* etc., especially after immunosuppression before transplantation)
Posttransplant infections in destroyed lung
Sinus infection in cystic fibrosis and ciliary dysfunction syndromes
Bronchiolitis obliterans:
Enhanced immunosuppression
Impaired clearance
Bronchiectasis

dition, however, is obliterative bronchiolitis. These patients usually are profoundly immunosuppressed, and their lung function and mucus clearance are often markedly impaired. Therefore, the most common cause of death in patients suffering from obliterative bronchiolitis is infections [4].

EPIDEMIOLOGY AND PREVENTION

Bacterial pneumonias are the most frequent infectious complications after lung transplantation. The reported incidences of bacterial pneumonia range from 35% to 66% [8, 10, 13, 14]. A significant number of the early episodes of bacterial pneumonia are caused by microorganisms cultivated from the donor lungs, as discussed below. Because their incidence during the first 2 postoperative weeks has decreased markedly because of antibiotic prophylaxis, most bacterial pneumonias occur in the intermediate and late postoperative period [13]. The overall cumulative incidence during the first year after transplant is ~70%, and it remains high beyond the first year (30%–40%). Nearly three-quarters of all bacterial pneumonias are caused by *Pseudomonas* species and Enterobacteriaceae [6, 7, 9, 13], and the remainder primarily by *Staphylococcus aureus*, *Enterococcus* species, and *Hemophilus influenzae*.

Infections by *Mycobacterium tuberculosis* are occasionally reported [15–18]. They may be due to reactivation [15], occult disease in the remaining native lung after single-lung transplantation [19], or transmission by the transplant [16–18]. One single case of nosocomial tuberculosis in a lung transplant recipient has been described [15]. Atypical mycobacteria are rarely found after lung transplantation [20, 21]. They usually present as indolent disease and respond well to treatment. One case of a fatal infection with *Mycobacterium chelonae* in a patient with severe obliterative bronchiolitis has been reported [21].

The second most common infectious complication after lung transplantation is CMV disease. The reported incidence in larger series ranges between 53% and 75% [22–25]. Thus, the occurrence of CMV infection and disease is much higher in lung transplant patients than in other solid-organ recipients. The rate of CMV pneumonitis is high not only in the D+/R− patients (90%–100%) but—in contrast to other solid-organ transplantations—also in the D±/R+ patients, in whom the incidence of severe disease is ~60%. Fatal cases are not rare. Thus, an effective prophylaxis of this disastrous complication is highly warranted (see article by van der Bij and Speich [26], in this issue).

Herpes simplex virus (HSV) infections after lung transplantation are of special concern [10, 27, 28]. The incidence of HSV infections is up to 18% [27, 28]. Most infections are clinically

significant [27]. Severe HSV pneumonia occurs in ~10% of patients without prophylaxis. The fatality rate is 20% [10, 28]. Most infections are due to reactivation and may occur as early as 5–10 days after transplantation. Single cases of primoinfection are described after renal transplantation. Prophylaxis with acyclovir reduces the incidence of HSV infections in immunosuppressed patients [29], and valacyclovir may even be superior. Thus, lung transplant recipients should receive 1 of these drugs for ~3 months postoperatively (A-II), if not already being treated with ganciclovir.

The incidence of Epstein-Barr virus (EBV)–related posttransplant lymphoproliferative disorders after lung transplantation varies greatly and ranges from 2% to 33% [11, 30–32]. In most cases, the disease originates in the lung allograft [30, 31]. Nonetheless, restriction fragment–length polymorphism analysis has shown that the neoplastic cells usually arise from the recipient's lymphocytes [33]. The risk for the development of posttransplant lymphoproliferative disorders is higher in EBV-negative lung transplant recipients [30], patients transplanted for cystic fibrosis [31], and recipients of lungs from donor with human leukocyte antigen status A2 and DR7 [32]. For further details, see article by Preikasaitis and Keay [34], in this issue.

The role of other viruses is not yet clear but may be relevant. Some centers have found a high incidence of nonherpes respiratory viruses [27, 35]. The attack rate, however, is <5% in most series. Rhinovirus infection sometimes causes mild upper respiratory tract disease in pediatric lung transplant recipients [36], but most cases are asymptomatic [27]. No permanent loss of respiratory function has been seen [27, 36]. Parainfluenza virus infections with significant pulmonary involvement and promotion of obliterative bronchiolitis have been described [27, 35, 36]. There is only 1 report of a severe influenza virus pneumonia in a pediatric lung transplant recipient who was treated with amantadine and recovered, but later developed obliterative bronchiolitis [37]. Respiratory syncytial virus infections in lung transplant recipients are often asymptomatic [27, 38]. They may cause, however, mild respiratory illness particularly in the pediatric patients [35, 36]. Ground-glass opacities are seen in almost 70% of the patients [39]. Cases with severe pneumonia and recovery in about one-third of them after treatment with aerosolized ribavirin have been reported [35, 40–42]. Obliterative bronchiolitis develops in about half of the survivors [9, 39, 42]. Infection with adenovirus poses a serious problem in the pediatric lung transplant recipients [36]. The attack rate is almost 50%, and at least half of the patients die in respiratory failure because of diffuse alveolar damage induced by the virus [36]. Obliterative bronchiolitis develops uniformly in the survivors. Occasional cases of adults with adenovirus infections are documented [27, 42–44]. In most of them, the clinical course was fatal [38, 42–44]. The 4 survivors all developed obliterative bronchiolitis [27, 42]. Cases of donor-transmitted adenoviral infections have been described [36]. In conclusion, nonherpes viral respiratory infection may be serious in lung transplant recipients, causing respiratory failure and obliterative bronchiolitis in the survivors. With respect to the various case reports and in analogy to the promising results in bone marrow transplant recipients [45, 46], we recommend treatment with ribavirin, either oral, iv, or aerosolized, in cases with significant nonherpes viral respiratory tract infections (B-III).

Fungal infections still are common in lung transplant recipients. Colonization with *Aspergillus* species occurs in 22%–85% of lung transplant recipients at some time after transplantation [47–54]. There is no difference in frequency of postoperative colonization between patients with cystic fibrosis, who often harbor *Aspergillus* species in their airways before transplantation, and the recipients without cystic fibrosis [50, 51, 55]. Invasive aspergillosis occurs in 13%–26% of the colonized lung transplant recipients and is uniformly fatal [53, 54]. Some patients develop invasive disease without prior colonization [48]. The risk of invasive aspergillosis peaks within the first 6 postoperative months, but at least one-third of the cases occur later [48]. Invasive aspergillosis may arise in the native lung after single-lung transplantation, either immediately after transplant because of preexistent disease in pretransplant immunosuppressed recipients [19] or in patients with destroyed native lungs (emphysema, lymphangioleiomyomatosis) [8, 19, 51, 56–58]. Native lung pneumonectomy is advisable in the latter (B-III) [56]. Patients suffering from obliterative bronchiolitis are also predisposed to the occurrence of invasive aspergillosis [12, 51]. A semi-invasive form of aspergillosis involving the anastomosis site and the large airways is quite common in lung transplant recipients [47, 49, 54, 59]. Treatment with either amphotericin B or itraconazole is successful in most cases. Colonization with *Aspergillus* species and previous CMV disease are significant risk factors for the development of invasive aspergillosis [48, 54]. Both conditions portend a relative risk of 11 for invasive disease [48, 54]. Preemptive therapy of colonized patients with oral itraconazole is highly recommended (A-II) and may completely prevent the development of invasive disease [49]. Semi-invasive tracheobronchial aspergillosis may develop despite treatment and can be cured by increasing the itraconazole dosage up to 400 mg b.i.d., with the goal of serum levels >1000 μg/L [49]. In 2 studies comparing a historical control group with patients treated with inhaled amphotericin B up to 20 mg t.i.d., the cumulative incidence of infections with *Aspergillus* species could be reduced significantly [60]. Whereas one report did not specify the rate of infection and disease, the second group found a decrease in the incidence of invasive aspergillosis from 15% (2/13 patients) to 0 (52 patients; $P = .038$). Thus, primary prophylaxis with inhaled amphotericin B may be considered in lung transplant recipients (B-II).

Most invasive infections with *Candida* species occur during

the first postoperative month, and most of them are transmitted via the donor organ (see below). The most common presentations are candidemia [61], necrotizing bronchial anastomotic infection [62], mediastinitis [14], and aortic anastomotic infection and disruption after heart-lung transplantation [63].

The incidence of *Pneumocystis carinii* pneumonia varies greatly between centers [6, 7, 64, 65]. A prevalence of up to 88% has been described in patients not receiving prophylaxis [64]. About two-thirds of the episodes are detected in asymptomatic patients by routine bronchoscopy and bronchoalveolar lavage. The organisms may stem from the recipient in cases with pretransplant immunosuppression. Prophylaxis with cotrimoxazole is nearly 100% effective [9, 11, 65] and therefore highly recommended (A-I). Inhaled pentamidine may be an alternative in patients not tolerating sulfa drugs (B-III). About one-third of the infections with *P. carinii* may occur after the first postoperative year [65]. Therefore, life-long prophylaxis is recommended by many centers (B-II), or, if discontinued, prophylaxis should be reinstituted in any patient receiving augmented immunosuppression (B-II).

Toxoplasma gondii pneumonitis has been described exclusively in heart-lung recipients [66]. There was 1 case of reactivation and 1 of primoinfection; both were diagnosed serologically, but not biopsy-proven. So far, no cases have been reported in recipients of lung transplants.

DIAGNOSTIC CONSIDERATIONS

Lung transplant recipients with fever or any organ dysfunction should undergo aggressive diagnostic work-up [2]. Blood cultures should be obtained routinely (A-II), because up to 25% of patients suffer from bloodstream infections during the early or late postoperative course [61]. *S. aureus, Pseudomonas aeruginosa*, and *Candida* species are the most common bloodstream isolates. In patients with respiratory symptoms or signs, bronchoscopy, bronchoalveolar lavage, and transbronchial lung biopsy should be performed immediately (A-II). Its diagnostic yield is almost 70% [67]. Inspection of the airways may reveal anastomotic problems or tracheobronchial aspergillosis. Bronchoalveolar lavage is very sensitive for most pathogens. Transbronchial biopsy is the only means to diagnose acute rejection and CMV pneumonitis [68–70]. Its sensitivity and specificity is almost 100%. Computed tomography may be helpful in the differential diagnosis of bilateral infiltrative lung diseases and detect mediastinal, bronchial, or vascular complications [71].

Most centers now perform routine surveillance bronchoscopies after lung transplantation [68–70] (B-II). Besides the early detection of asymptomatic significant acute rejection episodes or CMV pneumonitis in ~20%–30% of procedures, it allows the early identification of cases colonized by *Aspergillus*. Regular examination of peripheral blood for CMV by pp65 antigen detection or PCR has become routine in almost all centers (A-II).

LUNG TRANSPLANT DONOR

Almost all donor lungs harbor microorganisms at the time of organ procurement [72]. In ~40% of the recipients, these organisms can subsequently be isolated, and in ~20% of them, bronchopneumonia develops as a result of the respective organisms [73]. Deaths in lung transplant recipients because of donor-transmitted bacterial pneumonia have been described [72]. Thus, the bacteriological examination of bronchial washings of the donor lung is a prerequisite for the management of subsequent invasive infection in the transplant recipients (A-II). Even the growth of normal oral flora in the donor is considered to be a risk factor for early bacterial pneumonia in the recipient [14]. We recommend that antibiotic coverage in lung transplant recipients should be initiated with a broad-spectrum agent (A-II) and modified on the basis of cultures obtained from the donor lungs (A-II) [73], except in recipients with cystic fibrosis, who should be treated with an antimicrobial combination therapy tailored according to the pretransplant sputum cultures for ~2 weeks (A-III), as discussed below. In 1 series, this approach reduced the incidence of early postoperative bacterial pneumonia from 33% in a historical control group to 13% ($P = .005$) [13, 14].

Fiber-optic bronchoscopy with microbiologic sampling should be performed routinely in the lung donor [74] (A-III). The finding of a positive Gram stain, purulent secretions, or minor infiltrates on the chest X-ray is no obstacle for accepting the lungs for transplantation [75, 76] (B-II), and the results of transplantation utilizing these marginal donor organs have shown to be comparable to those using ideal transplants [77, 78]. Using these lungs for single-lung transplantation in recipients with pulmonary hypertension, however, is not advisable, because any postoperative allograft dysfunction may result in profound hypoxemia due to ventilation-perfusion mismatch, which is much more pronounced than in single-lung transplantations for other diseases [79] (D-III). Significant pneumonia and gross aspiration are generally considered to be a reason for exclusion [78] (E-III). There is experimental evidence that antibiotic treatment of donors with bacterial contamination prevents pneumonia in canine lung recipients [80]. Thus, antimicrobial treatment of human donors may decrease the risk of early bacterial pneumonia [78] (B-III).

Heavy growth of *Candida* species in the donor bronchus is a significant obstacle for accepting the organs for transplantation. The sequelae are mediastinitis, sepsis, or involvement of the great vessels leading to mycotic aneurysms and consecutive rupture. In 1 series, 3 of 4 recipients of lung transplants with heavy growth of *Candida* species developed mediastinitis,

which was uniformly fatal [14]. Thus, such donor organs should possibly be discarded (D-II). If they are nevertheless used, antifungal treatment with amphotericin should be instituted immediately (B-III) [14].

Unused donor lungs in cases of single-lung transplantation should undergo pathologic analysis (A-II) [81, 82], because they may show important unexpected findings such as pneumonia, emphysema, or pulmonary emboli. Moreover, the history of the donor is important to detect rare donor-related complications such as bone marrow or brain embolism.

RECIPIENT

Low-dose pretransplant corticosteroid treatment in the recipient has now proved to be acceptable, or even beneficial, and allows transplantation in patients who cannot be completely weaned from such therapy [83] (A-II); however, it has to be taken into account that in the case of single-lung transplantation the remaining native lung may harbor serious opportunistic infections such as invasive aspergillosis or *P. carinii* pneumonia [19, 58]. Thus, it is of the utmost importance to examine the excised recipient's lungs pathologically as quickly and thoroughly as possible (A-III), including microbiological analysis. If there is an invasive infection present, the transplant physician should be alerted, especially in the case of single lung transplantation, because the remaining native lung may harbor the same infection. The presence of an aspergilloma in the potential lung transplant recipient is often considered to be a contraindication for lung transplantation because of the danger of serious intraoperative bleeding. There are, however, no sound data on this issue, especially not in the setting of modern surgical techniques (D-III).

Computed tomography of the thorax should be performed routinely (A-III). It may help to detect mediastinal problems and intrapulmonary alterations such as abscesses or aspergillomas and other relevant findings with respect to transplant surgery. Computed tomography of the paranasal sinuses is recommended in patients with cystic fibrosis in order to detect invasive infections and potentially to plan pre- or posttransplant sinus surgery (A-III).

NATIVE LUNG

Several centers now report complications arising from the remaining native lung after single-lung transplantation, such as severe overinflation, perfusion mismatch, pneumothorax, and bacterial and fungal pneumonia. The incidence varies between 20% and 50% [8, 12, 19, 57, 84]. Morbidity and mortality are considerable, and many patients need additional surgery. Invasive aspergillosis of the native lungs is the most feared complication and often requires pneumonectomy [85]. The native lung in patients immunosuppressed during the pretransplant period, such as in cases of idiopathic pulmonary fibrosis, may harbor infectious agents such as *M. tuberculosis, P. carinii,* and *Aspergillus fumigatus,* which lead to serious exacerbations after transplantation.

CYSTIC FIBROSIS

As a consequence of the infectious nature of the pulmonary disease, the procedure of choice in patients with cystic fibrosis is double-lung transplantation [86]. Some centers still perform heart-lung transplantation in these patients with comparable results. Single-lung transplantation is considered not to be feasible; however, a few patients having undergone this procedure with concomitant contralateral pneumonectomy have been reported [87]. It is surprising that, despite the common presence of airway pathogens (*P. aeruginosa, S. aureus, Aspergillus* species) before transplantation, there is no evidence that patients with cystic fibrosis are at greater risk of infectious complications because of these organisms after lung transplantation than are other patients [51, 55, 88].

It has been shown from macrorestriction fragment pattern similarity that there is no change in the *P. aeruginosa* population in the airways of lung transplant recipients before and after transplantation [89]. Thus, it is assumed that the chronic drainage of *P. aeruginosa* into the lung allografts is caused by the bacterial reservoir in the paranasal sinuses and the trachea. The value of pre- or posttransplant sinus surgery in patients with cystic fibrosis, however, has not yet been established, but this procedure has been advocated by some centers [90–94] (B-III). It may reduce posttransplant bacterial infectious complications as has been shown in nontransplanted patients with cystic fibrosis [95].

Some centers consider the presence of a respiratory pathogen such as *P. aeruginosa* resistant to all antibiotics or other multiply resistant bacteria including *Burckholderia cepacia, Stenotrophomonas maltophilia,* or *Alcaligenes xylosoxidans* a contraindication to lung transplantation; however, this idea is not based on solid evidence [86]. Synergy testing of antimicrobial pairs in checkerboard dilutions of clinically achievable drug concentrations may inhibit most of the multiply resistant strains [96]. Patients colonized with *B. cepacia* are of special concern in 2 ways: first, most series demonstrate an increased posttransplant morbidity and mortality because of overwhelming pneumonia or sepsis caused by this organism [94]. Second, transmission between patients of *B. cepacia* is well documented [97], and this may adversely influence the center-specific epidemiological situation from a microbiological point of view. It seems, however, that there are different strains of *B. cepacia* regarding its aggressiveness and transmissibility. Thus, the decision to accept

patients with cystic fibrosis colonized by *B. cepacia* depends on the center-specific situation [98].

Infection with nontuberculous mycobacteria occurs in some patients with cystic fibrosis. This seems not to be a contraindication for lung transplantation (B-III), because in most reported cases these organisms can no more be isolated postoperatively [55].

References

1. Arcasoy SM, Kotloff RM. Lung transplantation. N Engl J Med **1999**; 340:1081–91.
2. Trulock EP. Lung transplantation. Am J Respir Crit Care Med **1997**; 155:789–818.
3. Hosenpud JD, Bennett LE, Keck BM, et al. The Registry of the International Society for Heart and Lung Transplantation: sixteenth official report, 1999. J Heart Lung Transplant **1999**; 18:611–26.
4. Boehler A, Kesten S, Weder W, et al. Bronchiolitis obliterans after lung transplantation: a review. Chest **1998**; 114:1411–26.
5. Bando K, Paradis IL, Komatsu K, et al. Analysis of time-dependent risks for infection, rejection, and death after pulmonary transplantation. J Thorac Cardiovasc Surg **1995**; 109:49–57.
6. Brooks RG, Hofflin JM, Jamieson SW, et al. Infectious complications in heart-lung transplant recipients. Am J Med **1985**; 79:412–22.
7. Dummer JS, Montero CG, Griffith BP, et al. Infections in heart-lung transplant recipients. Transplantation **1986**; 41:725–9.
8. Horvath J, Dummer S, Loyd J, et al. Infection in the transplanted and native lung after single lung transplantation. Chest **1993**; 104:681–5.
9. Kramer MR, Marshall SE, Starnes VA, et al. Infectious complications in heart-lung transplantation: analysis of 200 episodes. Arch Intern Med **1993**; 153:2010–6.
10. Maurer JR, Tullis DE, Grossman RF, et al. Infectious complications following isolated lung transplantation. Chest **1992**; 101:1056–9.
11. Paradis IL, Williams P. Infection after lung transplantation. Semin Respir Infect **1993**; 8:207–15.
12. Chaparro C, Maurer JR, Chamberlain D, et al. Causes of death in lung transplant recipients. J Heart Lung Transplant **1994**; 13:758–66.
13. Dauber JH, Paradis IL, Dummer JS. Infectious complications in pulmonary allograft recipients. Clin Chest Med **1990**; 11:291–308.
14. Zenati M, Dowling RD, Dummer JS, et al. Influence of the donor lung on development of early infections in lung transplant recipients. J Heart Transplant **1990**; 9:502–8.
15. Dromer C, Nashef SA, Velly JF, et al. Tuberculosis in transplanted lungs. J Heart Lung Transplant **1993**; 12:924–7.
16. Miller RA, Lanza LA, Kline JN, et al. Mycobacterium tuberculosis in lung transplant recipients. Am J Respir Crit Care Med **1995**; 152:374–6.
17. Ridgeway AL, Warner GS, Phillips P, et al. Transmission of *Mycobacterium tuberculosis* to recipients of single lung transplants from the same donor. Am J Respir Crit Care Med **1996**; 153:1166–8.
18. Schulman LL, Scully B, McGregor CC, et al. Pulmonary tuberculosis after lung transplantation. Chest **1997**; 111:1459–62.
19. Venuta F, Boehler A, Rendina EA, et al. Complications in the native lung after single lung transplantation. Eur J Cardiothorac Surg **1999**; 16:54–8.
20. Kesten S, Chaparro C. Mycobacterial infections in lung transplant recipients. Chest **1999**; 115:741–5.
21. Trulock EP, Bolman RM, Genton R. Pulmonary disease caused by *Mycobacterium chelonae* in a heart-lung transplant recipient with obliterative bronchiolitis. Am Rev Respir Dis **1989**; 140:802–5.
22. Duncan AJ, Dummer JS, Paradis IL, et al. Cytomegalovirus infection and survival in lung transplant recipients. J Heart Lung Transplant **1991**; 10:638–46.
23. Ettinger NA, Bailey TC, Trulock EP, et al. Cytomegalovirus infection and pneumonitis: impact after isolated lung transplantation. Washington University Lung Transplant Group. Am Rev Respir Dis **1993**; 147:1017–23.
24. Smyth RL, Scott JP, Borysiewicz LK, et al. Cytomegalovirus infection in heart-lung transplant recipients: risk factors, clinical associations, and response to treatment. J Infect Dis **1991**; 164:1045–50.
25. Soghikian MV, Valentine VG, Berry GJ, et al. Impact of ganciclovir prophylaxis on heart-lung and lung transplant recipients. J Heart Lung Transplant **1996**; 15:881–7.
26. van der Bij W, Speich R. Management of cytomegalovirus infection and disease after solid-organ transplantation. Clin Infect Dis **2001**; 33(Suppl 1):S32–7 (in this issue).
27. Holt ND, Gould FK, Taylor CE, et al. Incidence and significance of noncytomegalovirus viral respiratory infection after adult lung transplantation. J Heart Lung Transplant **1997**; 16:416–9.
28. Smyth RL, Higenbottam TW, Scott JP, et al. Herpes simplex virus infection in heart-lung transplant recipients. Transplantation **1990**; 49: 735–9.
29. Gold D, Corey L. Acyclovir prophylaxis for herpes simplex virus infection. Antimicrob Agents Chemother **1987**; 31:361–7.
30. Aris RM, Maia DM, Neuringer IP, et al. Post-transplantation lymphoproliferative disorder in the Epstein-Barr virus–naïve lung transplant recipient. Am J Respir Crit Care Med **1996**; 154:1712–7.
31. Cohen AH, Sweet SC, Mendeloff E, et al. High incidence of posttransplant lymphoproliferative disease in pediatric patients with cystic fibrosis. Am J Respir Crit Care Med **2000**; 161:1252–5.
32. Montone KT, Litzky LA, Wurster A, et al. Analysis of Epstein-Barr virus–associated posttransplantation lymphoproliferative disorder after lung transplantation. Surgery **1996**; 119:544–51.
33. Randhawa PS, Yousem SA. Epstein-Barr virus–associated lymphoproliferative disease in a heart-lung allograft: demonstration of host origin by restriction fragment-length polymorphism analysis. Transplantation **1990**; 49:126–30.
34. Preiksaitis JK, Keay S. Diagnosis and management of posttransplant lymphoproliferative disorder in solid-organ transplant recipients. Clin Infect Dis **2001**; 33(Suppl 1):S38–46 (in this issue).
35. Wendt CH, Fox JM, Hertz MI. Paramyxovirus infection in lung transplant recipients. J Heart Lung Transplant **1995**; 14:479–85.
36. Bridges ND, Spray TL, Collins MH, et al. Adenovirus infection in the lung results in graft failure after lung transplantation. J Thorac Cardiovasc Surg **1998**; 116:617–23.
37. Faul JL, Akindipe OA, Berry GJ, et al. Influenza pneumonia in a paediatric lung transplant recipient. Transpl Int **2000**; 13:79–81.
38. Matar LD, McAdams HP, Palmer SM, et al. Respiratory viral infections in lung transplant recipients: radiologic findings with clinical correlation. Radiology **1999**; 213:735–42.
39. Ko JP, Shepard JA, Sproule MW, et al. CT manifestations of respiratory syncytial virus infection in lung transplant recipients. J Comput Assist Tomogr **2000**; 24:235–41.
40. Doud JR, Hinkamp T, Garrity ER, Jr. Respiratory syncytial virus pneumonia in a lung transplant recipient: case report. J Heart Lung Transplant **1992**; 11:77–9.
41. Krinzman S, Basgoz N, Kradin R, et al. Respiratory syncytial virus-associated infections in adult recipients of solid organ transplants. J Heart Lung Transplant **1998**; 17:202–10.
42. Palmer SM Jr, Henshaw NG, Howell DN, et al. Community respiratory viral infection in adult lung transplant recipients. Chest **1998**; 113: 944–50.
43. Ohori NP, Michaels MG, Jaffe R, et al. Adenovirus pneumonia in lung transplant recipients. Hum Pathol **1995**; 26:1073–9.
44. Simsir A, Greenebaum E, Nuovo G, et al. Late fatal adenovirus pneumonitis in a lung transplant recipient. Transplantation **1998**; 65:592–4.
45. Sparrelid E, Ljungman P, Ekelöf-Andström E, et al. Ribavirin therapy in bone marrow transplant recipients with viral respiratory tract infections. Bone Marrow Transplant **1997**; 19:905–8.
46. Taylor CE, Osman HKE, Turner AJL, et al. Parainfluenza virus and respiratory syncytial virus infection in infants undergoing bone marrow

transplantation for severe combined immunodeficiency. Commun Dis Public Health **1998**; 1:202–3.
47. Brenier-Pinchart MP, Lebeau B, Devouassoux G, et al. Aspergillus and lung transplant recipients: a mycologic and molecular epidemiologic study. J Heart Lung Transplant **1998**; 17:972–9.
48. Cahill BC, Hibbs JR, Savik K, et al. Aspergillus airway colonization and invasive disease after lung transplantation. Chest **1997**; 112:1160–4.
49. Hamacher J, Spiliopoulos A, Kurt AM, et al. Pre-emptive therapy with azoles in lung transplant patients. Geneva Lung Transplantation Group [in process citation]. Eur Respir J **1999**; 13:180–6.
50. Nunley DR, Ohori P, Grgurich WF, et al. Pulmonary aspergillosis in cystic fibrosis lung transplant recipients. Chest **1998**; 114:1321–9.
51. Paradowski LJ. Saprophytic fungal infections and lung transplantation: revisited. J Heart Lung Transplant **1997**; 16:524–31.
52. Westney G, Maurer JR, de Hoyos A, et al. Aspergillus infections in lung transplant recipients. Am Rev Respir Dis **1993**; 147(Suppl 4):A600.
53. Westney GE, Kesten S, De Hoyos A, et al. Aspergillus infection in single and double lung transplant recipients. Transplantation **1996**; 61:915–9.
54. Yeldandi V, Laghi F, McCabe MA, et al. Aspergillus and lung transplantation. J Heart Lung Transplant **1995**; 14:883–90.
55. Flume PA, Egan TM, Paradowski LJ, et al. Infectious complications of lung transplantation: impact of cystic fibrosis. Am J Respir Crit Care Med **1994**; 149:1601–7.
56. Sandur S, Gordon SM, Mehta AC, et al. Native lung pneumonectomy for invasive pulmonary aspergillosis following lung transplantation: a case report. J Heart Lung Transplant **1999**; 18:810–3.
57. Speziali G, McDougall JC, Midthun DE, et al. Native lung complications after single lung transplantation for emphysema. Transpl Int **1997**; 10:113–5.
58. Stewart S, McNeil K, Nashef SA, et al. Audit of referral and explant diagnoses in lung transplantation: a pathologic study of lungs removed for parenchymal disease. J Heart Lung Transplant **1995**; 14:1173–86.
59. Kramer MR, Denning DW, Marshall SE, et al. Ulcerative tracheobronchitis after lung transplantation: a new form of invasive aspergillosis. Am Rev Respir Dis **1991**; 144:552–5.
60. Reichenspurner H, Gamberg P, Nitschke M, et al. Significant reduction in the number of fungal infections after lung-, heart-lung, and heart transplantation using aerosolized amphotericin B prophylaxis. Transplant Proc **1997**; 29:627–8.
61. Palmer SM, Alexander BD, Sanders LL, et al. Significance of blood stream infection after lung transplantation: analysis in 176 consecutive patients. Transplantation **2000**; 69:2360–6.
62. Palmer SM, Perfect JR, Howell DN, et al. Candidal anastomotic infection in lung transplant recipients: successful treatment with a combination of systemic and inhaled antifungal agents. J Heart Lung Transplant **1998**; 17:1029–33.
63. Dowling RD, Baladi N, Zenati M, et al. Disruption of the aortic anastomosis after heart-lung transplantation. Ann Thorac Surg **1990**; 49: 118–22.
64. Gryzan S, Paradis IL, Zeevi A, et al. Unexpectedly high incidence of *Pneumocystis carinii* infection after heart-lung transplantation. Am Rev Respir Dis **1988**; 137:1268–74.
65. Kramer MR, Stoehr C, Lewiston NJ, et al. Trimethoprim-sulfamethoxazole prophylaxis for *Pneumocystis carinii* infections in heart-lung and lung transplantation: how effective and for how long? Transplantation **1992**; 53:586–9.
66. Wreghitt TG, Hakim M, Gray JJ, et al. Toxoplasmosis in heart and heart and lung transplant recipients. J Clin Pathol **1989**; 42:194–9.
67. Chan CC, Abi Saleh WJ, Arroliga AC, et al. Diagnostic yield and therapeutic impact of flexible bronchoscopy in lung transplant recipients. J Heart Lung Transplant **1996**; 15:196–205.
68. Boehler A, Vogt P, Zollinger A, et al. Prospective study of the value of transbronchial lung biopsy after lung transplantation. Eur Respir J **1996**; 9:658–62.
69. Guilinger RA, Paradis IL, Dauber JH, et al. The importance of bronchoscopy with transbronchial biopsy and bronchoalveolar lavage in the management of lung transplant recipients. Am J Respir Crit Care Med **1995**; 152:2037–43.
70. Trulock EP, Ettinger NA, Brunt EM, et al. The role of transbronchial lung biopsy in the treatment of lung transplant recipients: an analysis of 200 consecutive procedures. Chest **1992**; 102:1049–54.
71. Soyer P, Devine N, Frachon I, et al. Computed tomography of complications of lung transplantation. Eur Radiol **1997**; 7:847–53.
72. Waller DA, Thompson AM, Wrightson WN, et al. Does the mode of donor death influence the early outcome of lung transplantation? A review of lung transplantation from donors involved in major trauma. J Heart Lung Transplant **1995**; 14:318–21.
73. Low DE, Kaiser LR, Haydock DA, et al. The donor lung: infectious and pathologic factors affecting outcome in lung transplantation. J Thorac Cardiovasc Surg **1993**; 106:614–21.
74. Riou B, Guesde R, Jacquens Y, et al. Fiberoptic bronchoscopy in brain-dead organ donors. Am J Respir Crit Care Med **1994**; 150:558–60.
75. Kron IL, Tribble CG, Kern JA, et al. Successful transplantation of marginally acceptable thoracic organs. Ann Surg **1993**; 217:518–22.
76. Shumway SJ, Hertz MI, Petty MG, et al. Liberalization of donor criteria in lung and heart-lung transplantation. Ann Thorac Surg **1994**; 57: 92–5.
77. Gabbay E, Williams TJ, Griffiths AP, et al. Maximizing the utilization of donor organs offered for lung transplantation. Am J Respir Crit Care Med **1999**; 160:265–71.
78. Sundaresan S, Semenkovich J, Ochoa L, et al. Successful outcome of lung transplantation is not compromised by the use of marginal donor lungs. J Thorac Cardiovasc Surg **1995**; 109:1075–9.
79. McCurry KR, Keenan RJ. Controlling perioperative morbidity and mortality after lung transplantation for pulmonary hypertension. Semin Thorac Cardiovasc Surg **1998**; 10:139–43.
80. Dowling RD, Zenati M, Yousem SA, et al. Donor-transmitted pneumonia in experimental lung allografts: successful prevention with donor antibiotic therapy. J Thorac Cardiovasc Surg **1992**; 103:767–72.
81. Husain AN, Hinkamp TJ. Donor lung pathology: correlation with outcome of transplanted contralateral lung [see comments]. J Heart Lung Transplant **1993**; 12:932–9.
82. Stewart S, Ciulli F, Wells FC, et al. Pathology of unused donor lungs. Transplant Proc **1993**; 25:1167–8.
83. Schäfers HJ, Wagner TOF, Demertzis S, et al. Preoperative corticosteroids: a contraindication to lung transplantation? Chest **1992**; 102: 1522–5.
84. Frost AE, Keller CA, Noon GP, et al. Outcome of the native lung after single lung transplant. Multiorgan Transplant Group. Chest **1995**; 107: 981–4.
85. Colquhoun IW, Gascoigne AD, Gould K, et al. Native pulmonary sepsis after single-lung transplantation. Transplantation **1991**; 52:931–3.
86. Yankaskas JR, Mallory GB, Jr. Lung transplantation in cystic fibrosis: consensus conference statement. Chest **1998**; 113:217–26.
87. Forty J, Hasan A, Gould FK, et al. Single lung transplantation with simultaneous contralateral pneumonectomy for cystic fibrosis. J Heart Lung Transplant **1994**; 13:727–30.
88. De Leval MR, Smyth R, Whitehead B, et al. Heart and lung transplantation for terminal cystic fibrosis: a 4 1/2-year experience. J Thorac Cardiovasc Surg **1991**; 101:633–41.
89. Walter S, Gudowius P, Bosshammer J, et al. Epidemiology of chronic *Pseudomonas aeruginosa* infections in the airways of lung transplant recipients with cystic fibrosis. Thorax **1997**; 52:318–21.
90. Davidson TM, Murphy C, Mitchell M, et al. Management of chronic sinusitis in cystic fibrosis. Laryngoscope **1995**; 105:354–8.
91. Laube I, Schoch OD, Holzmann D, et al. Beneficial effect of endoscopic sinus surgery in cystic fibrosis patients after lung transplantation. Am J Respir Crit Care Med **1999**; 159(Suppl 3):A54.
92. Lewiston N, King V, Umetsu D, et al. Cystic fibrosis patients who have undergone heart-lung transplantation benefit from maxillary sinus antrostomy and repeated sinus lavage. Transplant Proc **1991**; 23:1207–8.

93. Schulte DL, Kasperbauer JL. Safety of paranasal sinus surgery in patients with cystic fibrosis. Laryngoscope **1998**; 108:1813–5.
94. Snell GI, de Hoyos A, Krajden M, et al. *Pseudomonas cepacia* in lung transplant recipients with cystic fibrosis. Chest **1993**; 103:466–71.
95. Umetsu DT, Moss RB, King VV, et al. Sinus disease in patients with severe cystic fibrosis: relation to pulmonary exacerbations. Lancet **1990**; 335:1077–8.
96. Saiman L, Mehar F, Niu WW, et al. Antibiotic susceptibility of multiply resistant *Pseudomonas aeruginosa* isolated from patients with cystic fibrosis, including candidates for transplantation. Clin Infect Dis **1996**; 23:532–7.
97. Sun L, Jiang RZ, Steinbach S, et al. The emergence of a highly transmissible lineage of cbl+ *Pseudomonas (Burkholderia) cepacia* causing CF centre epidemics in North America and Britain. Nat Med **1995**; 1: 661–6.
98. Webb AK, Egan J. Should patients with cystic fibrosis infected with *Burkholderia cepacia* undergo lung transplantation? Thorax **1997**; 52: 671–3.